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(54) Title: METHODS FOR MONITORING PROTEASE INHIBITOR ANTIRETROVIRAL THERAPY

(57) Abstract: This invention relates to antiviral drug susceptibility and resistance tests to be used in identifying effective drug regimens for the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), particularly treatment regimes including a protease inhibitor. The invention further relates to the means and methods of monitoring the clinical progression of HIV infection and its response to antiretroviral therapy using phenotypic or genotypic susceptibility assays.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/01682

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12N 9/00, 9/50; C12Q 1/37

US CL :435/23, 183, 219

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/23, 183, 219

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS, MEDLINE, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,837,464 A (CAPON et al) 17 November 1998, see entire document.	1-6, 10-16 and 20-23
Y	YOUNG, B. et al. Resistance Mutations in Protease and Reverse Transcriptase Genes of Human Immunodeficiency Virus Type 1 Isolates from Patients with Combination Antiretroviral Therapy Failure. Journal of Infectious Diseases. November 1998, Vol. 178, No. 5, pages 1497-1501, see entire document.	1-6, 10-16 and 20-23

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

16 JUNE 2002

Date of mailing of the international search report

09 JUL 2002

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Form PCT/ISA/210 (second sheet) (July 1998)*

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HERTOGS et al. A Rapid Method for Simultaneous Detection of Phenotypic Resistance to Inhibitors of Protease and Reverse Transcriptase in Recombinant Human Immunodeficiency Virus Type 1 Isolates from Patients Treated with Antiretroviral Drugs. Antimicrobial Agents and Chemotherapy. February 1998, Vol. 42, No. 2, pages 269-276, especially page 270.	1-6, 10-16 and 20-23

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 10-16 and 20-23 (in-part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, 10-16, 20-23, drawn to a method of ·ssing the effectiveness of protease antiretroviral therapy by evaluating whether a sample contains a mutation at co· 82.
Group II, claim(s) 1-23, drawn to a method of assessing the effectiveness of protease antiretroviral therapy by evaluating whether a sample contains a mutation at codon 90.
Group III, claim(s) 24 and 25, drawn to a resistance test vector encoding a protease with a mutation at codon 82.
Group IV, claims 24 and 25, drawn to a resistance test vector encoding a protease with a mutation at codon 90.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Claim 1 is drawn to a method of assessing the effectiveness of antiretroviral therapy in an HIV-infected patient by evaluating whether a biological sample from the patient has a mutation at codon 82 and a secondary mutation and determining the change in susceptibility to a protease inhibitor. Lorenzi et al. (AIDS. 1997; 11 (12): F95-9, abstract only) teaches collecting samples from HIV-infected patients, sequencing the protease gene after drug therapy, and determining that non-responders developed mutations at codons 82 and 48, which confers resistance to antiviral drugs. Since neither the instant method steps nor the claimed mutations are novel in the art, it is determined that the instant claims lack unity of invention.
Group II is drawn to a second method of evaluating distinct mutations from group I.
Group III is drawn to a first product.
Group IV is drawn to a second product.